Scientists raise possibility of vaccine for Alzheimer's disease

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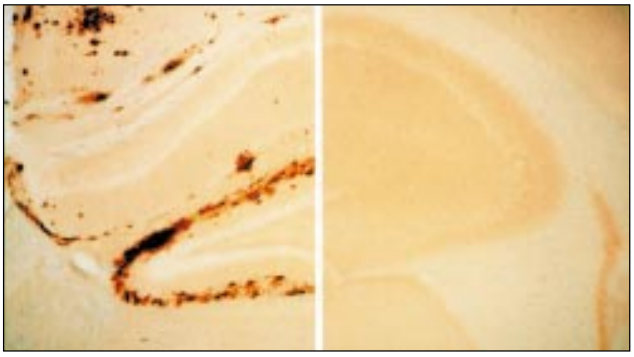

ELAN CORP/AP PHOTOS

Experimental Alzheimer's vaccine: the brain of a vaccinated mouse (right) shows less plaque formation than the control (left)

An experimental vaccine directed against amyloid, a protein implicated in Alzheimer's disease, has shown promise in animal trials (*Nature* 1999;400:173-7). The vaccine may lead to an effective treatment.

Scientists at Elan Pharmaceuticals developed a transgenic mouse model of Alzheimer's disease by injecting the rodent with a mutant form of the human amyloid precursor protein. The mutant amyloid precursor protein gene, which occurs in a number of familial forms of Alzheimer's disease, leads to an overexpression of the amyloid β peptide, the principal constituent of amyloid plaque in the disease.

Amyloid plaques consist of insoluble aggregates of amyloid protein and are thought to be involved in neuronal cell death.

The transgenic mice developed amyloid plaques in their brains in a manner specific to age and brain region, mimicking the changes seen in human forms of Alzheimer's disease.

The researchers then sought to see if immunisation with a fragment of amyloid protein would modify the disease in their affected mice. Accordingly, mice were immunised with a 42 amino acid segment of the amyloid B protein.

One group of mice was immunised at 6 weeks of age, when the neuropathological hallmarks of Alzheimer's disease are not yet present, and a second group at 11 months of age, when amyloid deposition is already prominent. Two main experiments were then conducted. In the first experiment (with the mice immunised at 6 weeks old), three control groups were used for comparison: one group received saline vaccinations, a second was left untreated, and the third was immunised with another plaque associated protein (serum amyloid protein).

At the age of 13 weeks, the groups vaccinated at 6 weeks were killed and their brains examined. Seven out of the nine mice treated with the β amyloid protein had no detectable plaques, whereas the other groups showed age related plaque accumulation.

In the second experiment (with the mice immunised at 11 months old) two control groups from the same litter were left untreated. At 18 months the vaccinated mice showed significantly less plaque formation than their 18 month old controls. They also had less gliosis and neuritic dystrophy. Even more striking, however, was the finding that these mice also had less plaque formation than younger untreated control mice, those at 12 months old.

This suggests that immunisation with the amyloid β protein facilitated the removal of amyloid plaque, probably by an antibody mediated immune attack.

Commenting on the study, Dale Schenk, the chief investigator on the project, said: "When we examined that group at 18 months … we expected to see widespread brain pathology [but] it had been halted in its tracks.

"The brain tissue looked essentially like [that of] the original 11 month old animal and in fact looked somewhat better. This suggested to us that the vaccine had potential for treatment."

The researchers said that the vaccine did not have any detectable side effects in mice.

Although the results are promising, it is not known if the findings are applicable to humans. Whether amyloid deposition is the cause or the effect of Alzheimer's disease is still widely debated.

Furthermore, although the mice developed plaques, they lacked other features of the disease, such as neurofibrillary tangles, and cognitive decline.

A spokesman for Elan Pharmaceuticals said that the company plans to submit an application to the US Food and Drug Administration and hopes to begin human clinical trials by the end of next year. □

Childhood thyroid cancers rise 10-fold in the Ukraine

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A dramatic rise in the incidence of childhood thyroid cancers has been noted in the Ukraine in the years since the 1986 Chernobyl nuclear disaster.

The nuclear accident, which occurred on 26 April 1986, involved a complete meltdown of the reactor at the Chernobyl atomic power plant. An estimated $4\text{-}5.4\times10^{16}$ becquerels (150-200 million curies) of radioactive material, including radioactive iodine, were released into the environment within the first 10 days of the accident. The highest concentration of radionuclides fell over the Ukraine, Belarus, and Russia, though raised levels were found as far away as North America.

Childhood radiation exposure is known to predispose to thyroid cancers. This was first noted in the 1940s and 1950s, when head and neck radiation for acne and tonsillar and adenoidal hypertrophy was common.

To study the effects of radiation further, researchers at the Institute of Endocrinology and Metabolism and at the Centre for Radiation Medicine at the Academy of Biomedical Sciences in Kiev, Ukraine, compiled a registry of all thyroid cancers in the area. Estimates of radiation dose were also made.

From 1981 to 1985, only 59 cases of thyroid cancers in children from birth to age 18 were recorded in the region. In contrast, 577 cases were identified from 1985 to 1997. The average number of cases per year also rose, from 12 in 1981-5 to 73 in 1996-7 (*Cancer* 1999;86:149-56).

Almost 80% of patients received less than 0.3 Gy of thyroid irradiation, but nearly 12% were exposed to over 1.0 Gy.

Epidemiologically, the rate of paediatric thyroid carcinomas rose more than 10-fold from 0.04 per 100 000 children in 1981 to 0.45 per 100 000 in 1996-7. Sixty four per cent of the thyroid cancers found in children 15 years and younger occurred in the most contaminated areas, the provinces of Kiev, Chernigev, Zhitomir, Cherkassy, and Rovno, further confirming the link between radiation dose and risk of thyroid cancer.

Almost 80% of the patients were under 10 years old when the accident occurred, and 42% were under 4 years old at the time. The young age reflects a time of peak vulnerability of the thyroid to ionising radiation.

Increases in thyroid cancer were also noted, however, in the adolescent population. In the age group 15-18 years 34 cases were diagnosed during 1981-5 and 219 during 1986-97. Meanwhile, the average age at diagnosis is increasing as years since the accident increase.

The authors state: "The increase in age at diagnosis is due to cancer affecting children who were aged less than five years in 1986. Hence this is the group at maximum risk because of the extreme sensitivity of the young thyroid to ionizing radiation."

Histologically, most of the cancers diagnosed were of the papillary carcinoma type. The researchers plan a 20 year follow up of 50 000 patients to assess further the effect of the Chernobyl fallout on the development of thyroid cancer. □